Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed (Certiva™)

DESCRIPTION

Certiva™ (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) is a sterile combination of diphtheria, tetanus, and pertussis toxoids (one pertussis antigen, inactivated pertussis toxin), adsorbed onto aluminum hydroxide.[1] It is intended for intramuscular injection only. After shaking, Certiva™ is a homogeneous white suspension.

The pertussis toxin (PT) is isolated from Phase 1 *Bordetella pertussis* grown in modified Stainer-Scholte medium. After purification by affinity chromatography, which includes the use of fetuin, a bovine serum protein, as an affinity ligand, PT is detoxified using hydrogen peroxide.

Diphtheria toxin is derived from *Corynebacterium diphtheriae* grown in Stainer's Diphtheria Culture Medium, containing casein hydrolysate, and is purified by fractional precipitation with ammonium sulfate. Tetanus toxin is derived from *Clostridium tetani* grown in modified Mueller and Miller Medium, containing casein hydrolysate, and is purified by precipitation with ammonium sulfate.[2] The purified diphtheria and tetanus toxins are detoxified using formaldehyde.

Each antigen is individually adsorbed onto aluminum hydroxide.[2] Each 0.5 ml dose of vaccine is formulated to contain 15 Lf diphtheria toxoid, 6 Lf tetanus toxoid, 40 mcg pertussis toxoid, 0.5 mg aluminum as aluminum hydroxide, and is preserved with 0.01% thimerosal (mercury derivative). The product may contain residual fetuin. The residual free formaldehyde content by assay is less than or equal to 10 ppm. The diphtheria and tetanus toxoids each induce not less than 2 units of antitoxin per ml in the guinea pig potency test. The potency of the pertussis

toxoid is evaluated by measurement of antibody titers to pertussis toxin in immunized mice using an ELISA.

Diphtheria and tetanus toxoid bulks for further manufacturing use are produced by Statens Seruminstitut, Copenhagen, Denmark. The pertussis toxoid is manufactured by North American Vaccine, Inc., Beltsville, Maryland. Final formulation and release of Certiva™ are conducted by North American Vaccine, Inc.

CLINICAL PHARMACOLOGY

Immunization against diphtheria, tetanus and pertussis, using a conventional whole-cell pertussis DTP vaccine (Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed) has been routine practice during infancy and childhood in the United States since the late 1940s. Widespread immunization in the United States has played a major role in dramatically reducing the incidence of cases and deaths from each of these diseases.[3]

Diphtheria

Diphtheria is a disease resulting from infection of the respiratory tract or skin with *Corynebacterium diphtheriae*. The disease can be localized to the site of infection or can be associated with systemic toxicity, which may include myocarditis and neuritis and is caused by diphtheria exotoxin, an extracellular protein metabolite of toxigenic strains of *C. diphtheriae*. Humans are the only known reservoir for *C. diphtheriae*. More than 200,000 cases of diphtheria, primarily among children, were reported in the United States in 1921, before the general use of diphtheria toxoid vaccine.[3] Approximately 5-10% of cases were fatal; the highest case-fatality rates were in the very young and the elderly. Immunization programs with diphtheria toxoid introduced in the 1940's had a significant impact on the epidemiology

of the disease. Only 24 cases of respiratory diphtheria were reported in the United States from 1980 to 1989, and 15 cases from 1990 to 1994; however, the case-fatality rate has remained constant at about 5-10%.[3,4] Although diphtheria is currently a rare disease in the United States, the disease has remained endemic in many developing countries and recent outbreaks have occurred in areas of the former Soviet Union.[5]

A complete vaccination series with diphtheria toxoid substantially reduces the risk and severity of disease, and protection is thought to last for at least 10 years.[3] Serum antitoxin concentrations of at least 0.01 antitoxin units per ml are generally regarded as protective.[6,7] Vaccination does not eliminate carriage of *C. diphtheriae* from the pharynx, nose, or skin.[3] Efficacy of the diphtheria toxoid used in Certiva™ was determined on the basis of immunogenicity studies, with a comparison to a serological correlate of protection (≥0.01 antitoxin units per ml) established by the Panel on Review of Bacterial Vaccines and Toxoids.[7] In a clinical study with Certiva™, 99.7% of 299 U.S. infants had protective titers to diphtheria toxin (≥0.01 antitoxin units per ml) in sera obtained one month after the third dose; vaccination at 2, 4, and 6 months of age.

Tetanus

Tetanus is a disease characterized by neuromuscular dysfunction resulting from the effects of a potent exotoxin elaborated by *Clostridium tetani*, a microorganism which is commonly found in the outdoor environment (usually soil). Persons with the disease exhibit muscular rigidity and spasms that can either be localized or generalized, depending on host factors and the site of inoculation. With the routine use of tetanus toxoid, the occurrence of tetanus in the United States has decreased markedly, from 560 reported cases in 1947 to an average of 57 cases

reported annually from 1985-1994.[3,4] Tetanus in the United States is primarily a disease of older adults. Of 99 cases with complete information reported to the Centers for Disease Control and Prevention during 1987-1988, 68% were ≥50 years of age, only 6 were <20 years of age. No cases of neonatal tetanus were reported. Overall, the case fatality rate was 21%. The disease continues to occur almost exclusively among persons who are unvaccinated or inadequately vaccinated or whose vaccination histories are unknown or uncertain.[8]

Spores of *C. tetani* are ubiquitous. Serologic tests indicate that naturally acquired immunity to tetanus toxin does not occur in the United States. Thus, universal primary immunization with subsequent maintenance of adequate antitoxin levels by means of timed boosters is needed to protect all age groups.[3] Tetanus toxoid is a highly effective antigen, and a completed primary series generally induces protective levels of at least 0.01 antitoxin units per ml, a level which has been reported to be protective.[7] It is thought that protection persists for at least 10 years.[3,9] Efficacy of the tetanus toxoid in Certiva™ was determined on the basis of immunogenicity studies with a comparison to a serological correlate of protection (≥0.01 antitoxin units per ml) established by the Panel on Review of Bacterial Vaccines and Toxoids.[7] In a clinical study with Certiva™, 100% of 299 U.S. infants had a protective level of tetanus toxoid (≥0.01 antitoxin units per ml) in sera obtained one month after the third dose; vaccination at 2, 4, and 6 months of age.

Pertussis

Pertussis (whooping cough) is a disease of the respiratory tract caused by *Bordetella pertussis*. Pertussis is highly communicable (attack rates in unimmunized household contacts of up to 90% have been reported) and can cause severe disease, particularly among the very

young.[3] Since immunization against pertussis became widespread, the number of reported cases and associated mortality in the United States have declined from an average annual incidence and mortality of 150 cases and 6 deaths per 100,000, respectively, in the early 1940's, to annual reported incidences of 1.6, 2.6, and 1.8 cases per 100,000 population in 1992, 1993, and 1994, respectively, and estimated annual incidences of 2.0 and 2.4 cases per 100,000 population for 1995 and 1996, respectively.[10,11] Precise epidemiologic data do not exist because bacteriological confirmation of pertussis can be obtained in less than half of the suspected cases. Most reported illness from *B. pertussis* occurs in infants and young children in whom complications can be severe. From 1980 to 1989, of 10,749 pertussis cases reported nationally in infants less than 1 year of age, 69% were hospitalized, 22% had pneumonia, 3% had seizures, 0.9% had encephalopathy, and 0.6% died.[12] Older children and adults, in whom classic signs are often absent, may go undiagnosed and may serve as reservoirs of disease.[13]

Routine vaccination with whole-cell DTP vaccine has significantly reduced pertussis-related morbidity and mortality. However, concerns regarding reactogenicity of whole-cell DTP vaccine have spurred development of safer pertussis vaccines. The role of different components produced by *B. pertussis* in either the pathogenesis of, or the immunity to, pertussis is not well understood. Certiva™-EU, which contains one pertussis antigen, pertussis toxoid, has been shown to be effective in preventing World Health Organization (WHO)-defined pertussis after three doses of vaccine administered at 3, 5, and 12 months of age.

Efficacy

Between 1991-1994, a double-blind, randomized, placebo-controlled efficacy trial of Certiva™-EU was conducted in Göteborg, Sweden, where pertussis is endemic and pertussis immunization had been stopped in 1979. Certiva™-EU contains the same amount of pertussis toxoid (40 mcg) per dose as Certiva™, but contains more diphtheria toxoid (25 Lf vs. 15 Lf) and more tetanus toxoid (7 Lf vs. 6 Lf) per dose than Certiva™. A total of 3,450 healthy infants from 96 Child Health Centers were randomized to receive Certiva™-EU (n=1,724) or Statens Seruminstitut Diphtheria and Tetanus Toxoids Adsorbed Vaccine (DT) (n=1,726) at 3, 5, and 12 months of age.[14,15] Cases of pertussis were identified by obtaining nasopharyngeal cultures for *B. pertussis* and acute and convalescent serum samples in all subjects and family members with coughing episodes lasting ≥ 7 days. Duration of cough and severity of symptoms were determined by telephone interview and/or office visit at approximately 4 weeks and again at 60 days after report of cough lasting ≥ 7 days.

The main observation period started 30 days after the third dose of vaccine and lasted a mean of 17 months. During this period, WHO-defined pertussis (paroxysmal cough for ≥ 21 days with one or more of the following: positive culture, positive culture in a family member, or a significant rise in serum PT-IgG or FHA-IgG) was identified in 72 (4.3%) of 1,682 Certiva™-EU recipients and 240 (14.3%) of 1,676 DT recipients.[14,15,16] Case rates per 100 person-years of follow-up were 2.89 in the Certiva™-EU group and 10.17 in the DT group. Starting one month after the third dose, the protective efficacy of Certiva™-EU against WHO-defined pertussis was 72% (95% CI: 62% to 78%). Protective efficacy against WHO-defined pertussis for the period starting 30 days after the second dose of vaccine up until

administration of the third dose was 60% (95% CI: 13% to 83%) (10 cases in 1,708 Certiva™-EU recipients, 25 cases in 1,717 DT recipients).[15]

When the definition of pertussis was expanded to include clinically milder disease with respect to type and duration of cough, with infection confirmed by culture and/or serologic testing, the efficacy of Certiva™-EU during the main observation period was 63% (95% CI: 52% to 71%) against ≥ 21 days of any cough and 54% (95% CI: 43% to 64%) against ≥ 7 days of any cough.[14] After the main observation period, follow-up was continued for an additional 6 month period during which the study was unblinded. During this period the efficacy of Certiva™-EU remained high against WHO-defined pertussis at 77% (95% CI: 65% to 85%) in children whose median age was then 36.5 months.[15,17]

Protective efficacy was also estimated in vaccine recipients who had household exposure to WHO-defined pertussis during the main observation period. Nineteen (19) of 88 Certiva™-EU recipients and 50 of 63 DT recipients were identified with a secondary case of pertussis (defined as paroxysmal cough for ≥ 21 days with infection confirmed by culture and/or serologic testing and with an onset between 6-60 days after onset in the primary case). The protective efficacy of Certiva™-EU in preventing WHO-defined pertussis after household exposure was 73% (95% CI: 57% to 86%) based on comparing the proportion of exposed subjects who were identified with pertussis in each vaccine group.[15,18]

Effectiveness

An epidemiologic, open-label, Mass Vaccination Project was initiated in June 1995 in the Göteborg region of Sweden to study the safety and effectiveness of Certiva™-EU and pertussis toxoid vaccines in infants and children. Effectiveness was determined by regional surveillance of pertussis cultures. Nasopharyngeal cultures were obtained from coughing individuals of all ages with suspected pertussis at the discretion of their treating physician. Cultures were analyzed by the single regional reference laboratory (Department of Clinical Bacteriology, Sahlgrenska Hospital, Göteborg, Sweden) as part of an established surveillance system from which pertussis culture data have been generated and reported since 1976. Table 1 depicts the monthly positive pertussis cultures collected from July 1989 through December 1997 (two and one half years into the project). Between 1989 and 1994 (the period before initiation of the Mass Vaccination Project), the yearly number of positive pertussis cultures varied, ranging from 575 out of 2,934 total cultures to 1,081 out of 4,272 total cultures. By the second year of the Mass Vaccination Project (July 1996 - June 1997), a total of 108 out of 784 cultures were positive for pertussis, the majority from children not participating in the Project with the remainder from children having received at least 1 dose of vaccine. During the next 6 months (July 1997 - December 1997), 30 cultures out of a total of 299 were pertussis positive, the majority from children not participating in the Project.

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TABLE 1

POSITIVE PERTUSSIS CULTURES IN THE GÖTEBORG REGION OF SWEDEN (1989-1997)

Year / Month	Before Pertussis Immunization*						Period of Mass Immunization with Certiva™-EU and Pertussis Toxoid		
	1989-1990	*1990-1991*	*1991-1992*	*1992-1993*	*1993-1994*	*1994-1995*	*1995-1996*	*1996-1997*	*1997-*
July	61	78	55	52	90	67	104	14	3
August	44	92	55	72	100	96	100	37	6
September	54	70	56	73	86	70	75	18	11
October	84	130	60	82	99	78	93	8	7
November	97	105	61	66	126	96	100	8	3
December	76	62	35	66	88	118	53	8	0
January	76	121	58	78	138	113	48	9	-
February	59	102	40	72	86	55	30	1	-
March	60	81	37	81	75	50	28	2	-
April	51	73	18	92	50	85	15	1	-
May	73	64	41	69	88	69	22	1	-
June	47	46	59	92	55	63	8	1	-
Total Positive	782	1024	575	895	1081	960	676	108	*30*
Total Cultures	3150	3801	2934	3608	4272	4105	2809	784	*299*

*National recommendation for routine pediatric pertussis vaccination reinstituted January 1996

Immune Response to Certiva™

In a study of Swedish infants comparing Certiva™ to Certiva™-EU, serum antibody levels to PT after three doses of Certiva™ administered at 2, 4, and 6 months of age (n=116) were significantly higher than those after two doses of Certiva™-EU administered at 3 and 5 months of age (n=103), but were significantly lower than those observed after three doses of Certiva™-EU administered at 3, 5, and 12 months of age (n=101).[15] The antibody response to PT after a fourth dose of Certiva™ administered at 15 months of age (n=114) was similar to that after the third dose of Certiva™-EU at 12 months of age (n=101).[15] In a study of U.S. infants, serum antibody titers to PT following four doses of Certiva™ administered at 2, 4, 6, and 15-21 months of age (n=89) were similar to those achieved following three doses of Certiva™-EU administered at 3, 5, and 12 months of age [subset of Swedish children from the efficacy trial (n=232)].[15] While a serologic correlate of protection for pertussis has not been established, the antibody response to PT in U.S. infants after doses of Certiva™ at 2, 4, 6, and 15-21 months of age was comparable to that achieved in Swedish infants in whom efficacy was demonstrated after three doses of Certiva™-EU at 3, 5, and 12 months of age.

Immune Response To Simultaneously Administered Vaccines

In a clinical study conducted in the United States, infants received Certiva™ at 2, 4, and 6 months of age, and at each time point, the majority were simultaneously immunized with *Haemophilus influenzae* type b conjugate vaccine (HibTITER, 96-99%), polio vaccine live oral (OPV) (83-97%), and hepatitis B vaccine (18-80%). Immune responses to these simultaneously administered vaccines were evaluated in a subset. After a third dose of OPV, 95-96% of infants had protective neutralizing antibody to poliovirus types 1 and 3 (n=219).[15]

After the third dose of HibTITER, 61% of infants achieved anti-PRP antibody levels ≥ 1 mcg/ml (n=249), compared to 73% of infants (n=77) who received HibTITER simultaneously with whole-cell DTP in the same study; these rates (61% vs. 73%) are not significantly different (p=0.078), but the study design lacked statistical power (80%) to rule out a difference of 15% (α=5%). After two doses of hepatitis B vaccine administered concurrently with Certiva™, 99% had anti-HBsAg titers ≥ 10 mIU/ml (n=101)[15]; the total number of hepatitis B vaccine doses received by these infants is unknown, because the number of doses received prior to entry into the study at 2 months of age was not recorded.

One-hundred thirty-three (133) infants who received 3 doses of Certiva™ in the above study received a fourth dose of Certiva™ at 15-21 months of age and were simultaneously immunized with measles, mumps, and rubella (MMR) vaccine and HibTITER. Anti-PRP antibody levels ≥ 1.0 mcg/ml were achieved in 100% of subjects (n=84); antibodies to measles, mumps, and rubella were detected in 91-95% of subjects (n=55).[15]

In another study of 221 children who received Certiva™ at 4 to 6 years of age, 89% and 16% simultaneously received polio, and measles, mumps, and rubella vaccination, respectively. Antibodies to measles, mumps and rubella were detected in 100% of tested subjects (n=32) and neutralization titers to polio types 1, 2, and 3 were achieved in 99% of tested subjects (n=105; 102 with OPV and 3 with inactivated polio vaccine).[15]

INDICATIONS AND USAGE

Certiva™ is indicated for active immunization against diphtheria, tetanus, and pertussis (whooping cough) in infants and children 6 weeks to 7 years of age (prior to seventh birthday).

Completion of a primary series of pertussis vaccination early in life is strongly recommended because of the substantial risks of complications of pertussis in infancy.[3]

This product is not recommended for immunizing persons on or after their seventh birthday (See **DOSAGE AND ADMINISTRATION**).

In instances where the pertussis vaccine component is contraindicated, Diphtheria and Tetanus Toxoids Adsorbed (For Pediatric Use) (DT) should be used for each of the remaining doses (See **CONTRAINDICATIONS**).

Tetanus Immune Globulin (Human TIG) and/or equine Diphtheria Antitoxin should be used if passive immunization is required.[3]

Individuals who have recovered from culture-confirmed pertussis do not need additional doses of Certiva™ but should receive additional doses of DT to complete the recommended immunization series.

Certiva™ is not to be used for treatment of actual infection with diphtheria, tetanus or pertussis.

As with any vaccine, vaccination with Certiva™ may not protect 100% of recipients.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine, including thimerosal (a mercury derivative), is a contraindication (See **DESCRIPTION**).

It is a contraindication to use this vaccine after an immediate anaphylactic reaction temporally associated with a previous dose. Because of uncertainty as to which component of the vaccine

might be responsible, no further vaccination with any diphtheria, tetanus or pertussis component should be carried out. Alternatively, because of the importance of tetanus vaccinations, such individuals may be referred for evaluation by an allergist.[3]

The decision to administer or delay vaccination because of a current or recent febrile illness depends largely on the severity of the symptoms and their etiology. Although a moderate or severe febrile illness is sufficient reason to postpone vaccinations, minor illnesses such as mild upper-respiratory infections with or without low-grade fever are not contraindications.[3,19,20,21,22] Elective immunization procedures should be deferred during an outbreak of poliomyelitis.[23]

Data on the use of Certiva™ in children for whom whole-cell pertussis vaccine is contraindicated are not available. Until such data are available, it would be prudent to consider CDC Advisory Committee on Immunization Practices (ACIP) and American Academy of Pediatrics (AAP) contraindications to pertussis-containing vaccines as contraindications to Certiva™.[3,20,21]

The ACIP states that "if either of the following events occurs after administration of DTaP or whole-cell DTP, subsequent vaccination with DTaP or whole-cell DTP is contraindicated"[22]:

- An immediate anaphylactic reaction.
- Encephalopathy not attributable to another identifiable cause (e.g., an acute, severe central nervous system disorder occurring within 7 days after vaccination and generally consisting of major alterations in consciousness, unresponsiveness, or generalized or focal seizures that persist more than a few hours, without recovery within 24 hours.) In such cases, DT vaccine should be administered for the remaining doses in the vaccination schedule to ensure protection against diphtheria and tetanus.

WARNINGS

The ACIP and AAP state that if any of the following events occur in temporal relation to receipt of DTP or DTaP, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered. There may be circumstances, such as a high incidence of pertussis, in which the potential benefits outweigh possible risks, particularly because these events have not been proven to cause permanent sequelae. The following events were previously considered contraindications and are now considered precautions by the ACIP[22]:

- Temperature of ≥105°F (≥40.5°C) within 48 hours, not attributable to another identifiable cause.
- Collapse or shock-like state (hypotonic hyporesponsive episode) within 48 hours.
- Persistent crying lasting ≥3 hours, occurring within 48 hours.
- Convulsions with or without fever, occurring within 3 days.

Data on the use of Certiva™ in children with a personal history of convulsion or an evolving or changing disorder of the central nervous system are not available. In the opinion of the manufacturer, the presence of a personal history of convulsion or an evolving or changing disorder of the central nervous system is considered a warning against further immunization with this vaccine.

The ACIP and AAP recommend considering deferral of immunization against pertussis in children with progressive neurologic disorder, personal history of convulsion, and known or suspected neurologic conditions which predispose to seizures or neurologic deterioration until

the child's health status has been fully assessed, a treatment regimen established and the condition stabilized.[3,20,21,22]

Children with a personal or family history of convulsion may have an increased risk of seizure following DTP vaccination compared with children without such histories.[24,25] However, the ACIP recognizes in certain instances that infants and children with stable neurologic conditions, including well-controlled seizures, may be vaccinated and that the occurrence of single seizures (temporally unassociated with DTP) does not contraindicate DTP vaccination if the seizures can be satisfactorily explained. In addition, the ACIP does not consider a family history of convulsions or other central nervous system disorders to be a contraindication to pertussis vaccination.[20,22,25] Data on the use of Certiva™ in these infants and children are not available.

The decision to administer a pertussis-containing vaccine to children with stable central nervous system disorders, such as well-controlled seizures or satisfactorily explained single seizures, must be made by the attending physician on a case-by-case basis, taking into account all relevant factors and an assessment of the potential risks and benefits for each child. The physician should review the full text of the ACIP and AAP guidelines prior to considering vaccination for such children. In addition, the parent or guardian should be advised of the potential increased risk involved (See **INFORMATION FOR VACCINE RECIPIENTS AND PARENTS**).

For children at higher risk of seizures than the general population, the ACIP recommends that acetaminophen or ibuprofen may be administered at the time of DTaP vaccination and for 24 hours thereafter (using an age-appropriate dose and dosing interval) to reduce the possibility of post-vaccination fever.[22]

A committee from the Institute of Medicine (IOM) has concluded that evidence is consistent with a causal relationship between whole-cell DTP and acute neurologic illness, and under special circumstances, between whole-cell DTP and chronic neurologic disease in the context of the National Childhood Encephalopathy Study (NCES) report.[26,27] However, the IOM committee concluded that evidence was insufficient to indicate whether or not whole-cell DTP vaccine increased the overall risk of chronic neurological disease.[27] The ACIP indicated that the results of the NCES were insufficient to determine whether DTP administration before the acute neurological event influenced the potential for neurologic dysfunction 10 years later.[20] Acute encephalopathy or permanent neurological injury have not been reported in clinical trials after administration of Certiva™, but experience with this vaccine is insufficient to rule this out (See **ADVERSE REACTIONS**).

Certiva™ should not be given to infants or children with thrombocytopenia or any coagulation disorder that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration. If the decision is made to administer Certiva™ to children with coagulation disorders, it should be given with caution (See **DRUG INTERACTIONS**).[19]

PRECAUTIONS

Care is to be taken by the physician for the safe and effective use of this vaccine.

1. Prior to administration of any dose of Certiva™, the physician should review the child's medical history. The physician should also review the child's previous immunization history for possible vaccine sensitivity and occurrence of any symptoms or signs of an adverse event after immunization, in order to determine the existence of any contraindication to

immunization with Certiva™ and to allow an assessment of benefits and risks (See **CONTRAINDICATIONS** and **ADVERSE REACTIONS**).

2. Before the injection of any biological, the physician should take all precautions known for the prevention of allergic or any other side reactions, including understanding the use of the biological concerned and the nature of the side effects and adverse reactions that may follow its use. Epinephrine injection (1:1,000) and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.
3. Children with impaired immune responsiveness, whether due to the use of immunosuppressive therapy (including irradiation, corticosteroids, antimetabolites, alkylating agents, and cytotoxic agents), a genetic defect, human immunodeficiency virus (HIV) infection, or other causes, may have reduced immune response to active immunization procedures. Deferral of immunization may be considered in individuals receiving immunosuppressive therapy. Other groups should receive this vaccine according to the usual recommended schedule (See **DRUG INTERACTIONS**).[28]
4. Certiva™ is not contraindicated based on the presence of HIV infection.[3]
5. Special care should be taken to ensure that the injection does not enter a blood vessel.
6. A separate, sterile syringe and needle or a sterile disposable unit should be used for each subject to prevent transmission of hepatitis or other infectious agents from person to person. Needles should not be recapped but should be disposed of properly.

Caution: the packaging stopper of this product contains natural rubber latex which may cause allergic reactions.

INFORMATION FOR VACCINE RECIPIENTS AND PARENTS

Parents or guardians of infants and children to be vaccinated should be fully informed of the benefits and risks of vaccination with Certiva™ and the importance of completing the immunization series, unless contraindicated.

The physician should inform the parents or guardians about the potential for adverse reactions that have been temporally associated with Certiva™ and other pertussis vaccine administrations.

The parents or guardians of infants and children with family history of convulsions or other central nervous system disorders should be advised of the potential increased risk of seizures following DTP vaccinations.

Prior to each immunization, the parent or guardian should be provided with the Vaccine Information Materials (VIMs), as required by the National Childhood Vaccine Injury Act of 1986.[29] Parents or guardians should be instructed to report any severe or unusual reactions to their health-care provider.

The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including, but not limited to, the reporting of events required by the National Childhood Vaccine Injury Act of 1986.[29,30] The toll-free number for VAERS forms and information is 1-800-822-7967.

DRUG INTERACTIONS

For information regarding simultaneous administration with other vaccines, refer to **DOSAGE AND ADMINISTRATION** and **CLINICAL PHARMACOLOGY**.

As with other intramuscular injections, the vaccine should not be given to infants or children on anticoagulant therapy, unless the potential benefit clearly outweighs the risk of administration (see **WARNINGS**).

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (administered in greater than physiologic doses), may reduce the immune response to vaccines. Although no specific studies with pertussis-containing vaccines under these circumstances are available, if immunosuppressive therapy will be discontinued shortly, it would be reasonable to defer immunization until the patient has been off therapy for at least one month; otherwise, the patient should be vaccinated while still on therapy.[3,28] If Certiva™ has been administered to persons receiving immunosuppressive therapy, receiving a recent injection of immune globulin or having an immunodeficiency disorder, an adequate immunologic response may not be obtained.

Tetanus Immune Globulin, or Diphtheria Antitoxin, if used, should be given in a separate site, with a separate needle and syringe.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

Certiva™ has not been evaluated for its carcinogenic or mutagenic potentials or impairment of fertility.

PREGNANCY

REPRODUCTIVE STUDIES - PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with Certiva™. It is not known whether Certiva™ can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Certiva™ is NOT recommended for use in a pregnant woman. This vaccine is not recommended for persons 7 years of age or older (See **PEDIATRIC USE**).

PEDIATRIC USE

SAFETY AND EFFECTIVENESS OF Certiva™ IN INFANTS BELOW 6 WEEKS OF AGE HAVE NOT BEEN ESTABLISHED (SEE **DOSAGE AND ADMINISTRATION SECTION**).

THIS VACCINE IS NOT RECOMMENDED FOR PERSONS 7 YEARS OF AGE AND OLDER.

Tetanus and Diphtheria Toxoids Adsorbed for adult use (Td) is to be used in individuals 7 years of age or older.

ADVERSE REACTIONS

In clinical studies in the United States and Sweden, 11,560 doses of Certiva™ (10,608 intramuscular, 952 subcutaneous) and 30,951 doses of Certiva™-EU (5,574 with thimerosal; 25,377 without thimerosal; all subcutaneous) have been administered.[15] In these studies, 3,698 infants received 10,615 doses of Certiva™ as a 3-dose series at 2, 4, and 6 months of age; 682 of these infants received a 4th consecutive dose of Certiva™ at 15-24 months of age; no children have received 5 consecutive doses of Certiva™. Forty-two (42) children received Certiva™ as a 4th dose at 15-22 months of age, following 3 doses of whole-cell DTP vaccine; 221 children received Certiva™ as a 5th dose at 4-6 years of age, following 3 doses of whole-cell DTP and a 4th dose of whole-cell DTP or acellular DTaP vaccine. In addition, 1,875 infants received 5,574 doses of Certiva™-EU as a 3-dose series at 3, 5 and 12 months of age.[14,15] In an ongoing study, 11,859 infants are completing a 3-dose series at 3, 5, and 12 months of age and have been evaluated after 25,377 doses to date.[15] In a comparative study, local and systemic adverse reactions commonly associated with whole-cell DTP vaccination occurred less frequently after vaccination with Certiva™.[15] Studies have shown, however, that the rate of erythema, swelling, and fever increased with successive doses of Certiva™ (Tables 2, 3, and 6).

In a double-blind safety and immunogenicity study in the United States, 1,303 infants were randomized to receive Certiva™ (n=977) or U.S. licensed whole-cell DTP vaccine manufactured by Lederle Laboratories (n=326) at 2, 4, and 6 months of age. At each time point, 96-99% of subjects also received *Haemophilus influenzae* type b conjugate vaccine, 83-97% received polio vaccine live oral, and 18-80% received hepatitis B vaccine. Safety data were actively collected using standardized diary cards and follow-up telephone calls at 1, 3, and

7 days after each vaccination, and are available for 972 and 323 infants, respectively, who received at least one dose of Certiva™ or whole-cell DTP. Local injection site reactions and systemic reactions such as fever (≥ 38°C), irritability, decreased appetite, and drowsiness were significantly less frequent after Certiva™ than after whole-cell DTP (Table 2). Within 7 days after vaccination, there were no deaths and five hospitalizations (3 Certiva™ recipients: 1 with cold/high fever on day 6, 1 with ear infection on day 6, 1 with febrile seizure and respiratory infection on day 4; 2 whole-cell DTP recipients: 1 with diarrhea on day 4, 1 with hives/allergic reaction on day 4), none judged to be vaccine-related by the investigators.[15]

418

419 TABLE 2

420 ADVERSE EVENTS (%) OCCURRING WITHIN 72 HOURS AFTER INTRAMUSCULAR VACCINATION OF

421 U.S. INFANTS WITH CERTIVA™ OR WHOLE-CELL DTP AT 2, 4, AND 6 MONTHS OF AGE

	Certiva™ Reaction %			Whole-Cell Pertussis DTP Reaction %			p-values*
	Dose 1 2 Mos.	Dose 2 4 Mos.	Dose 3 6 Mos.	Dose 1 2 Mos.	Dose 2 4 Mos.	Dose 3 6 Mos.	Combined Doses DTaP:DTP
Local *n*=	*972*	*898*	*868*	*323*	*295*	*279*	*2,738 : 897*
Redness (any)	5.2	8.5	13.0	22.1	29.9	27.2	<0.0001
Redness ≥ 3 cm	0.2	0.6	1.3	5.6	1.4	2.2	<0.0001
Swelling (any)	8.0	8.6	8.6	29.9	23.4	20.4	<0.0001
Swelling ≥ 3 cm	1.9	1.2	1.3	14.0	9.2	5.0	<0.0001
Tenderness/pain	8.4	6.8	5.4	28.6	15.9	18.0	<0.0001
Systemic‡							
Fever ≥ 38°C†	3.2	7.2	11.4	15.7	19.7	25.5	<0.0001
Fever ≥ 39°C†	0.2	1.7	2.1	0	2.5	7.1	NS (p=0.052)
Irritability	34.2	30.3	27.0	55.4	38.6	34.8	<0.0001
Drowsiness	38.3	21.2	12.4	45.2	25.1	20.4	<0.001
Decreased appetite	14.5	11.7	9.2	22.0	10.5	14.3	<0.01
Vomiting	14.3	8.2	7.3	13.3	7.5	6.5	NS
High-pitched/unusual crying	0.3	0	0.1	0.6	0	0	NS#
Persistent crying ≥ 3 hours	0.1	0.1	0	0.6	0	0	NS#
Hypotonic-hyporesponsive episode	0.1**	0	0	0	0	0.7	NS#
Seizures/convulsions	0	0	0	0	0	0.4	NS#

422 * Two-tailed Fisher's exact test/Certiva™:whole-cell DTP across all doses

423 ‡ Other age-appropriate vaccines concomitantly administered with Certiva™

424 † Rectal temperatures only, denominators for Certiva™ at doses 1, 2 and 3 are 524, 363 and 282, respectively, and for whole-

425 cell DTP 172, 122 and 98, respectively, for a total of 1,169 Certiva™ doses and 392 whole-cell DTP doses

426 # NS = not significant (p>0.05); study not powered to detect significant differences for the predicted event rates

427 **Database record represents one subject after dose 1; no medical attention sought, child received doses two, three and four

428 without incident

In an open-label study in the United States, safety results are available from 2,480 infants who received at least one dose of a three-dose series of Certiva™ administered at 2, 4, and 6 months of age. At each time point, 95-98% of subjects also received *Haemophilus influenzae* type b conjugate vaccine, 71-94% received polio vaccine live oral, and 7-50% received hepatitis B vaccine. Safety data were actively collected using standardized diary cards and follow-up telephone calls at 1, 2, 3, and 7 days after each vaccination (Table 3). Within 7 days after vaccination, there were no reports of seizures, hypotonic-hyporesponsive episodes (HHE), or deaths; seven hospitalizations occurred (bronchiolitis, RSV pneumonia, pyelonephrosis, urinary tract infection, breath-holding episode, stridor, otitis media/fever), none of which were judged to be vaccine-related by the investigators.[15] Of the 2,283 infants who completed the 3-dose series, 316 received a 4th dose at 15-24 months of age. Standardized diary cards and telephone follow-up at 2 and 7 days post-vaccination were used to actively collect safety data. There were no reports of serious adverse events during the first 7 days after vaccination. The most common complaints were irritability, injection site redness (of any size) and pain (Table 3).[15]

443 TABLE 3

444 ADVERSE EVENTS (%) OCCURRING WITHIN 72 HOURS AFTER INTRAMUSCULAR VACCINATION

445 OF U.S. INFANTS WITH CERTIVA™ AT 2, 4, AND 6, AND 15-24 MONTHS OF AGE

	Certiva™			
	Dose 1 2 Mos.	Dose 2 4 Mos.	Dose 3 6 Mos.	Dose 4 15 Mos.
Local *n**=	*2480*	*2374*	*2283*	*316*
Redness (any)	4.4	7.7	10.9	21.0
Redness ≥ 3 cm	0.2	0.3	0.5	5.7
Swelling (any)	3.6	5.4	7.9	12.7
Swelling ≥ 3 cm	0.6	0.4	1.1	4.5
Tenderness/pain (any)**	5.9	4.0	3.9	19.0
Systemic‡				
Fever ≥ 38°C†	1.5	3.5	5.0	10.5
Fever ≥ 39°C†#	0.1	0.4	1.0	2.6
Irritability	33.4	27.9	26.4	22.5
Drowsiness	33.5	17.1	11.1	11.4
Decreased appetite	15.4	10.5	10.0	8.9
Vomiting/spitting up	7.3	4.9	4.5	3.8
High-pitched, unusual crying	0.2	0.1	0	0
Persistent crying ≥ 3 hours#	0.1	0.04	0	0

446 * Denominators vary less than 1.2% from the column totals

447 ** 85% of events reported were mild in intensity

448 ‡ Other age-appropriate vaccines concomitantly administered with Certiva™

449 † Rectal temperatures only, fever rates based on 6,447 total Certiva™ doses at 2, 4 and 6 months of age, and 266

450 at 15 months of age

451 # Within 48 hours of vaccination, there were no fevers ≥40.3°C (rectal) and no persistent, inconsolable crying ≥ 3

452 hours

In an open-label study, 175 children who had previously received either whole-cell DTP (n=42) or Certiva™ (n=133) at 2, 4, and 6 months of age were immunized with Certiva™ at 15-21 months of age. Standardized diary cards and telephone follow-up at 2 and 7 days post-vaccination were used to actively collect safety data (Table 4).

TABLE 4

ADVERSE EVENTS (%) OCCURRING WITHIN 72 HOURS FOLLOWING AN INTRAMUSCULAR DOSE OF CERTIVA™ AT 15-21 MONTHS OF AGE IN CHILDREN WHO RECEIVED THREE DOSES OF CERTIVA™ OR WHOLE-CELL DTP VACCINE AT 2, 4, AND 6 MONTHS OF AGE[15]

	Vaccine received at 2, 4, and 6 mo. of age	
	Certiva™	Whole-cell DTP
EVENTS *n*=	*133*	*42*
Local (any)		
Redness	15.3	7.1
Swelling	9.9	9.5
Pain	9.0	7.1
Systemic*		
Fever ≥ 38°C‡	2.1	15.4
Decreased appetite	9.8	14.3
Vomiting	3.8	0
Drowsiness	7.5	14.3
Irritability	19.6	21.4
High-pitched/unusual crying	0	0
Persistent crying ≥ 3 hours	0.8†	0

* Other age-appropriate vaccines concomitantly administered with Certiva™

‡ Denominators for rectal temperatures for Certiva™ primed and whole-cell DTP primed subjects are 48 and 13, respectively; 38°C =100.4°F

† Represents one subject who was bitten by ants

Table 5 lists the frequency of adverse reactions in 221 U.S. children who received Certiva™ at 4-6 years of age. These children had previously received 3 doses of a whole-cell DTP vaccine at 2, 4, and 6 months of age and either a whole-cell DTP or DTaP vaccine at 12-24 months of age.

TABLE 5

ADVERSE EVENTS (%) OCCURRING WITHIN 7 DAYS FOLLOWING AN INTRAMUSCULAR DOSE OF CERTIVA™ AT 4-6 YEARS OF AGE (5TH DOSE IN THE SERIES) IN 221 CHILDREN HAVING RECEIVED ALL OF THEIR PREVIOUS AGE-APPROPRIATE PERTUSSIS VACCINATIONS[15]

Local Events (any)			Systemic Events**				
Redness	Swelling	Pain*	Fever >38°C	Decreased Appetite	Vomiting	Drowsiness	Irritability
19.5	18.1	36.2	4.5	6.8	5.0	10.0	8.1

* 83% of subjects reported pain of mild intensity; the remaining 17% were of moderate intensity as judged by the caregiver

** Other age-appropriate concomitantly administered with Certiva™

In the randomized, double-blinded, placebo-controlled efficacy trial in Göteborg, Sweden, a total of 3,450 infants were vaccinated with either DT (1,726 infants) or Certiva™-EU (1,724 infants) at 3, 5, and 12 months of age; no other vaccines were administered concurrently. Safety data were actively collected using standardized diary cards and telephone follow-up 7 days after each vaccination and monthly for general health and disease surveillance. Within 7 days after vaccination, there were no reports of hypotonic-hyporesponsive episodes or deaths; 28 hospitalizations (12 Certiva™-EU, 16 DT) occurred, none judged to be vaccine-related by the investigators. Rates of both fever and local injection site reactions increased with the number of vaccinations in both groups. Rates for fever were similar between the two groups within the first seven days following a vaccination. Injection site redness and swelling were more common among Certiva™-EU-vaccinated than among DT-vaccinated children after the second injection (Table 6).[14,15]

TABLE 6

ADVERSE EVENTS (%) OCCURRING AFTER SUBCUTANEOUS* VACCINATION OF SWEDISH INFANTS WITH CERTIVA™-EU AT 3, 5, AND 12 MONTHS OF AGE

	Dose 1 3 Mos.		Dose 2 5 Mos.		Dose 3 12 Mos.	
	Certiva™-EU	DT	Certiva™-EU	DT	Certiva™-EU	DT
n=	*1724*	*1726*	*1708*	*1717*	*1692*	*1687*
Within 7 days of vaccination						
Redness (any)	22.2	18.8	50.9	39.5	57.6	49.3
Redness ≥ 4 cm	0.1	0.2	2.0	0.8	10.0	7.9
Swelling (any)	10.8	10.5	34.7	28.7	45.9	38.9
Swelling ≥ 4 cm	0.2	0.2	1.9	0.9	9.1	6.7
Seizures**	0	0	0	0	0.2	0
Within 48 hours of vaccination						
Fever ≥ 38°C†	6.4	6.5	10.9	11.4	16.8	16.6
Fever ≥ 39°C†	0.5	0	1.4	0.8	2.5	2.3
Persistent crying ≧ 3 hrs	0.1	0.2	0.2	0.1	0	0

* Subcutaneous administration may result in an increased frequency of local injection site complaints when compared to intramuscular administration.[14] Certiva™ is for *intramuscular* injection only (see DESCRIPTION and DOSAGE AND ADMINISTRATION)

** Three febrile events: two with concomitant respiratory tract infection and one with concomitant gastroenteritis; no afebrile seizures were reported

† Rectal temperatures

Other adverse events (irritability, crying, feeding problems, vomiting, sleeping problems, respiratory infections, diarrhea and physician visits) were seen with similar frequency in the two groups after each vaccination.

When the total U.S. clinical trial experience with Certiva™ is considered (10,587 doses administered to 3,715 infants and children), adverse event rates per 1,000 doses meeting AAP and ACIP criteria as absolute contraindications or precautions to further pertussis immunization and occurring within 72 hours after immunization were: persistent, inconsolable crying for ≥ 3 hours, 0.57; fever ≥ 40.5°C, 0; seizures (febrile and afebrile), 0; hypotonic-hyporesponsive

episode, 0.09 (database record represents one subject after dose 1; no medical attention sought; child received doses 2, 3, and 4 without incident).

For Certiva™-EU (5,574 doses containing thimerosal administered to 1,875 Swedish infants with active follow-up) rates per 1,000 doses for similar adverse events occurring within 7 days of vaccination were the following: persistent crying for ≥ 3 hours, 1.44; fever ≥ 40.5°C, 1.79; seizures (febrile) within 48 hours of vaccination, 0.36; hypotonic-hyporesponsive episode, 0. Rates of serious adverse events that are less common than those reported in these actively monitored trials are not known at this time.

In an open-label study in Sweden, 11,859 infants have received 25,377 doses of Certiva™-EU (without thimerosal) at 3, 5, and 12 months of age, and serious adverse events were ascertained through evaluation of hospitalization databases and spontaneous reporting. Within 7 days after vaccination, there were three hospitalizations for seizures (2 within 48 hours after vaccination); no hospitalizations for diagnoses judged by the investigators to be consistent with hypotonic-hyporesponsive episodes; and two deaths attributed to Sudden Infant Death Syndrome (SIDS), neither judged to be vaccine-related.[15] In this study, 32,799 children 1-5 years of age have received 81,613 doses of a vaccine containing pertussis toxoid (but not the tetanus and diphtheria toxoids; 6,764 doses were administered as Certiva™-EU as the first dose at 1 year of age) on a 0, 2, and 8 month schedule, and were monitored the same way as the infants. Within 7 days after vaccination, there were seven hospitalizations for seizures (none within 48 hours after vaccination); no hospitalizations for diagnoses judged by the investigators to be consistent with hypotonic-hyporesponsive episodes; and no deaths.

In the overall clinical trial experience involving 17,690 infants and children who received 42,490 doses of Certiva™ or Certiva™-EU, there were no occurrences of anaphylaxis or encephalopathy. Nine deaths were reported, two occurring within 7 days after vaccination; none of these events was determined to be related to vaccination. Causes of death included four cases of Sudden Infant Death Syndrome (SIDS), 1 accidental suffocation, 1 invasive bacterial infection, 1 cerebral edema (unknown cause), 2 unknown (history of cardiac malformation or myelomeningocele).[15] The rate of SIDS was 0.6 per thousand infants vaccinated with Certiva™ in the U.S. studies, and 0.1 per thousand infants vaccinated with Certiva™-EU in Swedish studies.[15] The incidence of SIDS in Sweden from 1985 - 1992 was between 0.7 and 1.1 cases per thousand live births with a decline from 0.7 to 0.4 cases per thousand live births between 1992 and 1995.[31,32] From 1979 to 1996, the incidence of SIDS in the U.S. has declined from 1.5 to 0.74 cases per thousand live births.[33] By chance alone, some cases of SIDS can be expected to follow receipt of whole-cell DTP or DTaP.[21] In the clinical trial experience of 32,799 children who received 81,613 doses of pertussis toxoid vaccine, there were no reports of anaphylaxis or encephalopathy.[15] Of five reported deaths, none occurred within 7 days after vaccination and none was determined to be related to vaccination. Causes of death included 1 invasive bacterial infection, 1 unexpected sudden death, 1 murder, 1 hepatoblastoma, and 1 unknown (history of cardiac malformation).[15] Rarely, an anaphylactic reaction (*i.e.*, hives, swelling of the mouth, difficulty breathing, hypotension or shock) has been reported after receiving preparations containing diphtheria, tetanus, and/or pertussis antigens.[3]

Arthus-type hypersensitivity reactions, characterized by severe local reactions (generally starting 2 to 8 hours after an injection) may follow receipt of tetanus toxoid. A few cases of peripheral

neuropathy have been reported following tetanus toxoid administration, although the IOM concluded that the evidence is inadequate to accept or reject a causal relation.[34] A review by the IOM found a causal relation between tetanus toxoid and brachial neuritis and Guillain-Barré Syndrome.[34] The following illnesses have been reported as temporally associated with the administration of tetanus toxoid containing vaccines: neurological complications[35,36] including cochlear lesion[37], brachial plexus neuropathies[38], paralysis of the radial nerve[39], paralysis of the recurrent laryngeal nerve, accommodation paresis, and EEG disturbances with encephalopathy.[40,41] In the differential diagnosis of polyradiculoneuropathies following administration of a vaccine containing tetanus toxoid, tetanus toxoid should be considered as a possible etiology.[41]

Additional Adverse Reactions Evaluated in Conjunction with Whole-cell DTP Vaccination

Whole-cell DTP has been associated with acute encephalopathy.[27] In the National Childhood Encephalopathy Study (NCES), a large, case-control study in England, children 2 to 35 months of age with serious acute neurologic disorders (cases), such as encephalopathy or complicated convulsion(s), were compared to children without acute neurologic disorders who were matched for age, sex, and residence (controls).[42] Cases were more likely to have received whole-cell DTP vaccine within 7 days before onset of illness than were controls within 7 days before being the exact age as their matched case child at the time of onset of illness (relative risk, 3.3). The attributable risk for all neurologic events was estimated to be 1:140,000 doses of whole-cell DTP vaccine administered.[42]

A detailed follow-up to the NCES indicated that cases were significantly more likely than controls to have chronic nervous system dysfunction 10 years later.[43] These cases who

developed chronic nervous system dysfunction were more likely to have received whole-cell DTP vaccine within 7 days before onset of acute illness than were controls within 7 days before being the exact age as their matched case child at the time of onset of acute illness (relative risk, 5.5). A committee of the IOM has concluded that the evidence is consistent with a causal relation between whole-cell DTP and acute neurologic illness, and that the balance of the evidence is consistent with a causal relation between whole-cell DTP and the forms of nervous system dysfunction described in the NCES in those children who experience a serious acute neurologic illness within 7 days after receiving whole-cell DTP vaccine. However, the IOM committee also concluded that the evidence is insufficient to indicate whether or not whole-cell DTP increases the overall risk in children for chronic nervous system dysfunction.[27] The ACIP indicated that the results of the NCES were insufficient to determine whether whole-cell DTP administration before the acute neurological event influenced the potential for neurologic dysfunction 10 years later.[20] Subsequent studies have failed to provide evidence in support of a causal relationship between whole-cell DTP vaccination and either serious acute neurologic illness or permanent neurologic injury.[36,44,45,46]

Onset of infantile spasms has occurred in infants who have recently received whole-cell DTP vaccines or DT. Analysis of data from the NCES on children with infantile spasms showed that receipt of DT or whole-cell DTP vaccines was not causally related to infantile spasms.[26,47] The incidence of onset of infantile spasms increases at 3 to 9 months of age, the time period in which the second and third doses of vaccine are generally given. Therefore, some cases of infantile spasms can be expected to be related by chance alone to recent receipt of whole-cell DTP vaccine.[26,47]

Sudden Infant Death Syndrome (SIDS) has been reported in infants following administration of whole-cell DTP or DTaP vaccine. Large case-control studies of SIDS in the U.S. have shown that receipt of whole-cell DTP vaccine was not causally related to SIDS.[26,48,49] It should be recognized that the first three immunizing doses of whole-cell DTP vaccine or DTaP vaccine are usually administered to infants 2 to 6 months old and that approximately 85% of SIDS cases occur at ages 1 to 6 months, with the peak incidence occurring at 6 weeks to 4 months of age. By chance alone, some cases of SIDS can be expected to follow receipt of whole-cell DTP or DTaP vaccine.[48] A review by a committee of the IOM concluded that available evidence did not indicate a causal relation between whole-cell DTP vaccines and SIDS.[26]

A bulging fontanel associated with increased intracranial pressure which occurred within 24 hours following whole-cell DTP immunization has been reported, although a causal relationship has not been established.[26,35]

The above findings regarding possible association of unusual neurologic events and SIDS relate only to DTP vaccines containing whole-cell pertussis. At this time there are insufficient data to determine their relevance to Certiva™ immunization.

ADVERSE EVENT REPORTING

Adverse events occurring after vaccine administration should be reported by the health-care provider to the U.S. Department of Health and Human Services through the Vaccine Adverse Event Reporting System (VAERS).[30] The toll-free number for VAERS forms and information is 1-800-822-7967. The National Vaccine Injury Compensation Program, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health-care providers who administer vaccines to maintain permanent vaccination records (including a record of the name of the vaccine manufacturer, lot number of the vaccine administered, date of administration and the name, address and title of the person administering the vaccine) and to report occurrences of certain adverse events to the U.S. Department of Health and Human Services. Reportable events include those listed in the Act (*i.e.*, those listed in the Vaccine Injury Table) for each vaccine and events specified in the package insert as contraindications to further doses of the vaccine.[29,30]

The health-care provider also should report these events to the Director of Medical Affairs, North American Vaccine, Inc., 12103 Indian Creek Court, Beltsville, Maryland 20705, or call toll-free 1-888-NAVAVAX (1-888-628-2829).

DOSAGE AND ADMINISTRATION

General

The vaccine should be inspected visually for extraneous particulate matter and/or discoloration prior to administration. If these conditions exist, the vaccine should not be used.

Shake vial well to obtain a homogeneous suspension before withdrawing each dose. Inject 0.5 ml of Certiva™ intramuscularly only. The preferred injection sites are the anterolateral aspect of the thigh and the deltoid muscle of the upper arm. The vaccine should not be injected into the gluteal area or areas where there may be a major nerve trunk.

Before injection, the skin over the injection site should be cleansed with suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

Fractional doses (doses < 0.5 ml) should not be given since the safety and efficacy of fractional doses have not been determined.

IMMUNIZATION SERIES

A 0.5 ml intramuscular injection of Certiva™ is recommended for administration at 2, 4, and 6 months of age, at intervals of six to eight weeks, with a fourth dose given at 15-20 months of age (see CLINICAL PHARMACOLOGY). The interval between the third and fourth doses should be at least 6 months. The customary age for the first dose is two months of age, but the vaccine may be given starting at six weeks of age. It is recommended that Certiva™ be given for all doses in the series because no interchangeability data on DTaP vaccines exist.

Certiva™ may be used to complete the immunization series in infants who have received one or two doses of whole-cell DTP vaccine. However, the safety and efficacy of Certiva™ in such infants have not been evaluated.

Certiva™ as a fourth dose is recommended at 15-20 months of age in children who have received three doses of whole-cell DTP vaccine. The interval between the third and fourth dose should be at least 6 months.

Certiva™ as a fifth dose is recommended at 4-6 years of age (prior to the seventh birthday) in children who have received 4 doses of a whole-cell DTP vaccine or 3 doses of a whole-cell DTP vaccine followed by one dose of a DTaP vaccine. A fifth dose is not needed if the fourth dose was given on or after the fourth birthday. At this time, there are no data to establish the frequency of adverse events following a fifth dose of Certiva™ in children who previously received 4 doses of Certiva™.

ADDITIONAL DOSING INFORMATION

If any recommended dose of pertussis vaccine cannot be given, DT (For Pediatric Use) should be given as needed to complete the series.

Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved with Certiva™. There is no need to start the series over again, regardless of the time elapsed between doses.

A reduced or fractional dose (dose < 0.5 ml) should not be given, because the safety and efficacy of reduced doses have not been determined.[19]

Pre-term infants should be vaccinated according to their chronological age from birth.[19]

Persons 7 years of age or older should not be immunized with Certiva™. They should receive Tetanus and Diphtheria Toxoids (Td) for adult use for routine booster immunization against tetanus and diphtheria.

SIMULTANEOUS VACCINE ADMINISTRATION

In clinical trials, Certiva™ was routinely administered, at separate sites, concomitantly with one or more of the following vaccines: polio vaccine live oral (OPV), hepatitis B vaccine, *Haemophilus influenzae* type b conjugate vaccine (Hib), and measles, mumps and rubella vaccine (MMR) (see **CLINICAL PHARMACOLOGY**).

No data are available on the simultaneous administration of inactivated polio vaccine (IPV) as a primary series or varicella vaccine with Certiva™.

When concomitant administration of other vaccines is required, they should be given with different syringes and at different injection sites.

The ACIP encourages routine simultaneous administration of acellular DTaP, Hib, IPV or OPV, hepatitis B, MMR and varicella vaccines for children who are at the recommended age to receive these vaccines and for whom no specific contraindications exist at the time of the visit, unless, in the judgment of the provider, complete vaccination of the child will not be compromised by administering vaccines at different visits.[19,22] Simultaneous administration is particularly important if the child might not return for subsequent vaccinations.

HOW SUPPLIED

Vial, 15 Dose (7.5 ml) -- Product No. 40121

STORAGE

Store between 2-8° C (35-46° F). DO NOT FREEZE.

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May 1, 1998

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